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INTELLECTUAL PROPERTY INDIA

सत्यमेव जयते

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY
PATENT OFFICE, DELHI BRANCH
W - 5, WEST PATEL NAGAR
NEW DELHI - 110 008.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application*** *and* ***Complete Specification*** *filed in connection with Application for Patent No.* ***861/Del/2003*** *dated* ***01st July 2003.***

Witness my hand this 9th day of August 2004.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

FORM 1

THE PATENTS ACT, 1970

(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 5(2), 7, 54 and 135; and rule 39)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare -

(a) that we are in possession of an invention titled **"A PROCESS FOR THE PREPARATION OF SUSPENSION COMPOSITION OF CEFUROXIME AXETIL"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. SHASHIKANTH ISLOOR

b. ARCHANA KHOSA

c. SANJEEV SETHI

d. RAJIV MALIK

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. We claim the priority from the application(s) filed in convention countries, particulars of which are as follows: **NOT APPLICABLE**

5. We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: **NOT APPLICABLE**

6 We state that the application is divided out of our application, the particulars of which are given below and pray that this application deemed to have been filed on ..... Under section 16 of the Act. **NOT APPLICABLE**

7. That we are the assignee or legal representatives of the true and first inventors.

8. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18, Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana). INDIA.

9. Following declaration was given by the inventors or applicants in the convention country:
We, SHASHIKANTH ISLOOR, ARCHANA KHOSA, SANJEEV SETHI, RAJIV MALIK of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon 122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention or applicant in the convention country declare that the applicant herein, **Ranbaxy Laboratories Limited**, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a.

(SHASHIKANTH ISLOOR)

b. Archana Khosa
(ARCHANA KHOSA)

c.

(SANJEEV SETHI)

d.

(RAJEEV MALIK)

10. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

11. Followings are the attachment with the application:
- a. Complete Specification (3 copies)
- b. Drawings (3 copies)
- c. Priority document(s)
- d. Statement and Undertaking on FORM – 3
- e. Power of Authority (Not required)
- f. Fee Rs.**3,000**/- (Rupees Three Thousand only..) in cheque bearing No. dated : drawn on

We request that a patent may be granted to us for the said invention.

Dated this **30TH** day of **June, 2003.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

FORM 2 0861-03

01 JUL 2003

The Patents Act, 1970
(39 of 1970)

COMPLETE SPECIFICATION
(See Section 10)

A PROCESS FOR THE PREPARATION OF SUSPENSION COMPOSITION OF CEFUROXIME AXETIL

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to a dry powder pharmaceutical suspension composition of cefuroxime axetil suitable for use as a liquid suspension wherein the composition has better bioavailability and is free of food effect. It also relates to a process for the preparation of such a composition.

Cefuroxime axetil is a semi synthetic broad spectrum cephalosporin antibiotic for oral administration. Chemically, it is (RS)-1-hydroxyethyl (6R,7R)-7-[2-(2-furyl)glyoxylamido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate, 7^2-(Z)-(O-methyl-oxime),1 -acetate 3-carbamate. After oral administration, cefuroxime axetil is absorbed from gastrointestinal tract and rapidly hydrolysed to cefuroxime by nonspecific estrases present in the intestinal mucosa and blood. It is available as tablets and oral suspension under the brand name Ceftin® marketed by Glaxo. The oral suspension is available in dry powder form which, when constituted with water provides 125mg or 250mg of cefuroxime per 5mL of suspension. Ceftin® oral suspension is an alternative for dosing pediatric patients who can not swallow tablets.

As per Physician's Desk Reference (PDR), It has been reported that Ceftin® for oral suspension is not bioequivalent to Ceftin® tablets on a mg/mg basis. In a study conducted by Glaxo comparing the bioavailability of Cefuroxime axetil for oral suspension and tablet in adults, the AUC of suspension was found to be 91% of that of tablet, and the peak plasma concentration was found to be 71% of that of tablet. Consequently, it is not feasible to substitute oral tablet with oral suspension. The oral dosing with cefuroxime axetil suspension with improved bioavailability of cefuroxime would be convenient in cases of elderly patients who have difficulty in swallowing and also in medical conditions where the patient is not able to swallow a tablet.

It has also been suggested that Ceftin oral suspension should be taken with food. In a study comparing the effect of food on the bioavailability of cefuroxime axetil it was found that, Ceftin® oral suspension showed a delay in the time of the peak plasma concentration (T_{max}) under fed conditions than in fasting conditions. This is undesirable for effective therapy because the plasma levels necessary to show therapeutic effect are delayed and quick onset of action may not be achieved.

US Patent No. 4865851 describes the preparation of Ceftin® oral suspension comprising cefuroxime axetil in particulate form, the particles being provided with integral coatings of a lipid or a mixture of lipids like stearic acid and/or palmitic acid. The coated particles are prepared by atomizing a dispersion of particulate cefuroxime in the molten lipid and cooling the coated particles. The process is time consuming, requires complicated machinery to perform coating operations with strict control on process parameters like temperature and pressure. Also, without limiting to any theory, the lipid coating may retard the dissolution of cefuroxime axetil and delay it's absorption.

In the light of the foregoing, it would be advantageous to develop an oral suspension of cefuroxime axetil which not only provides improved bioavailability in comparison to Ceftin® oral suspension but is also free of food effects. Further, there is a need for a process for the preparation of such a suspension which is convenient, economical and requires simple machinery.

We have now discovered that dry powder pharmaceutical suspension composition of cefuroxime axetil can be prepared by granulating a mixture of cefuroxime axetil, lubricant and glidant. The granules when constituted as liquid suspension not only provides better bioavailability as compared to the marketed Ceftin® oral suspension but is also free of food effects. These granules may be administered as suspension or taken with a glass of water. Suspension of granules is particularly convenient for elderly patients.

The term "dry powder" as used herein includes any composition which is dry and flowable such as granules, flakes, spheroids and other forms which can be readily prepared and when added to an ingestible liquid and mixed, give the desired liquid suspension.

Therefore, in one general aspect, the present invention relates to a dry powder pharmaceutical suspension composition suitable for use as a liquid suspension comprising granules containing cefuroxime axetil, at least one lubricant and at least one glidant.

In another general aspect, it relates to a dry powder pharmaceutical suspension composition suitable for use as a liquid suspension comprising granules containing

cefuroxime axetil, at least one lubricant and at least one glidant wherein the said composition exhibits better bioavailability.

In another general aspect, it relates to a dry powder pharmaceutical suspension composition suitable for use as a liquid suspension comprising granules containing cefuroxime axetil, at least one lubricant and at least one glidant wherein the said composition exhibits better bioavailability and is free of food effects.

In another general aspect, it relates to a method of forming a dry powder pharmaceutical suspension composition suitable for use as a liquid suspension comprising:

granulating a mixture of cefuroxime axetil, at least one lubricant, at least one glidant by compaction/slugging; and
sizing the granules.

In another general aspect it relates to a method of forming a dry powder pharmaceutical suspension composition suitable for use as a liquid suspension comprising:

granulating a mixture of cefuroxime axetil, at least one lubricant, at least one glidant by compaction/slugging; and
sizing the granules; and
mixing with other pharmaceutical excipients.

In another general aspect, it relates to a method of dosing for infections treated with cefuroxime axetil which comprises administering the dry powder pharmaceutical suspension composition of cefuroxime axetil dissolved or suspended in an ingestible liquid, comprising granules containing cefuroxime axetil, at least one lubricant and at least one glidant.

Cefuroxime axetil as used herein may be in crystalline form or more preferably in amorphous form, for example, as described in GB 2127401 and is present in granules comprising a mixture of cefuroxime axetil, lubricant and a glidant and optionally other pharmaceutical excipients. The size of the granules is preferably less than 250μm. The cefuroxime axetil may comprise upto about 99.89% by weight of the granules.

The lubricants can be selected from stearic acid, calcium stearate, sodium stearyl fumarate and combinations thereof. The lubricant in the granules can be from about 0.01% to about 10% by weight of the granules.

The glidant can be selected from colloidal silicon dioxide and talc. The concentration of glidant can be from about 0.1% to about 5% by weight of the granules.

The oral suspension may comprise other pharmaceutical excipients such as suspending agents/viscosity enhancers, buffering agents, fillers, wetting agents, preservatives, flavouring agents and sweeteners.

The suspending agents/viscosity enhancers may be selected from cellulosic derivatives like hydroxypropyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, sodium carboxymethylcellulose; gums like xanthan gum, guar gum; polysaccharides like starch, pregelatinised starch; alginates like sodium alginate; acrylic acid copolymers like carbopols; polyvinylpyrrolidone and combinations thereof.

The buffering agent may be selected from monosodium citrate , sodium citrate , citric acid and combinations thereof.

The fillers may be selected from sucrose, starch, lactose, microcrystalline cellulose and combinations thereof.

The wetting agent may be selected from sodium lauryl sulphate, polysorbates like tween 40, tween 60, tween 80, poloxamer and combinations thereof.

The preservatives may be selected from methyl paraben, propyl paraben, sodium benzoate or a combination thereof.

The flavouring agents may be selected from grenadine flavour, tutti frutti flavour and peppermint flavour while the sweeteners may be selected from aspartame, saccharine sodium, sucrose, sorbitol and sodium cyclamate and combinations thereof.

The pharmaceutical composition as described herein may be presented as a suspension for administration, as a dry product for constitution with an ingestible liquid like water before use for administration as a suspension, or for direct administration and then washed down with water or other ingestible liquid. The dry powder for suspension can be packed in suitable containers to provide multidose or a single unit dose liquid suspension.

The dry powder pharmaceutical suspension may be prepared by the general procedure comprising dry blending cefuroxime axetil, at least one lubricant, at least one glidant; granulating by compaction/slugging; sizing and optionally mixing with other pharmaceutical excipients. These are then filled into a bottle or a suitable container in an amount suited to a dosage regimen. A suitable ingestible liquid, particularly water is added in an amount sufficient to provide cefuroxime axetil in desired dosage strength. Typically, the dry powder after constitution with an ingestible liquid is set to provide a liquid suspension containing 125mg or 250mg of cefuroxime axetil per 5mL of liquid suspension.

The dry powder pharmaceutical suspension composition is stable on storage and when constituted with an ingestible liquid for administration, the corresponding liquid suspension is stable for the duration the therapy is required.

As per one of the embodiments, the dry powder for cefuroxime oral suspension may be prepared by the following steps:

1. Cefuroxime axetil, stearic acid, colloidal silicon dioxide are blended in a suitable mixer;
2. The blend of step 1 is then granulated by compaction or slugging.
3. The granules of step 2 are sized and mixed with other optional excipient(s)
4. The final blend is packed in HDPE bottles.

The following example is provided to illustrate the invention but is by no means limiting it.

Example 1

Ingredients	Quantity/5mL
Cefuroxime axetil granules Cefuroxime axetil (eq. to 250mg Cefuroxime) Colloidal silicon dioxide Stearic acid	 315.78 6.0 6.0
Sucrose	3979.21
Aspartame	20.00
Silicon dioxide	84.00
Monosodium citrate	10.00
Flavour	19.00
Sodium chloride	10.00
Total weight	**4450.00**

Method:

Cefuroxime axetil, colloidal silicon dioxide and stearic acid were blended in a suitable mixer. The blend was compacted to form granules which were sized and screened through a BSS # 60 Sieve (250 microns). Sucrose, aspartame, silicon dioxide, monosodium citrate, flavour and sodium chloride were sifted and blended with the above cefuroxime axetil granules. The final blend was packed in high density polyethylene (HDPE) bottles.

Bioavailability studies:

The oral Cefuroxime axetil suspension of example 1 and Ceftin® oral suspension (Glaxo) were evaluated for pharmacokinetic parameters in 24 healthy human adult volunteers under fasting and fed conditions in separate comparative, randomized, single-dose (eq. to 500mg of cefuroxime), 2-way crossover bioavailability studies. Table 1 gives the details of the observed pharmacokinetic parameters in the study conducted under fasting conditions. Table 2 gives the details of pharmacokinetic parameters observed under fed conditions.

Table 1 Pharmacokinetic Parameters (mean values) of Oral Suspension of Example 1 and Ceftin® Oral Suspension in human volunteers following administration of a 500mg dose under fasting conditions.

	AUC_{0-t} (mcg.h/mL)	$AUC_{0-\infty}$ (mcg.h/mL)	C_{max} (mcg/mL)	T_{max} (hours)
Example 1 (Test)	22.394	22.764	6.421	1.966
Ceftin® Oral Suspension (Reference)	20.618	21.188	5.475	2.356

The oral suspension of example 1 (Test) under fasting conditions has shown higher values for both AUC_{0-t} as well as $AUC_{0-\infty}$ as compared to Ceftin® oral suspension. The AUC_{0-t} showed an increase of about 8.61% and $AUC_{0-\infty}$ showed an increase of about 7.43%. The C_{max} showed an increase of about 17.27%. The time of peak plasma concentration (T_{max}) was achieved about 0.39 hours earlier.

Table 2 Pharmacokinetic Parameters (mean values) of Oral Suspension of Example 1 and Ceftin® oral suspension in human volunteers following administration of a 500mg dose under fed conditions.

	AUC_{0-t} (mcg.h/mL)	$AUC_{0-\infty}$ (mcg.h/mL)	C_{max} (mcg/mL)	T_{max} (hours)
Example 1 (Test)	30.830	31.389	7.053	2.462
Ceftin® Oral Suspension (Reference)	24.622	27.163	4.737	4.667

The oral suspension of example 1 (Test) under fed conditions has shown higher values for both AUC_{0-t} as well as $AUC_{0-\infty}$ as compared to Ceftin® oral suspension. The AUC_{0-t} showed an increase of about 25.21% and $AUC_{0-\infty}$ showed an increase of about 15.55%. The C_{max} showed an increase of about 48.89%. The time of peak plasma concentration (T_{max}) was achieved about 2.2 hours earlier.

Table 3 Pharmacokinetic Parameters (mean values) of Oral Suspension of Example 1 and Ceftin® Tablet in human volunteers following administration of a 500mg dose under fed conditions.

	$AUC_{0-\infty}$ (mcg.h/mL)	C_{max} (mcg/mL)	T_{max} (hours)
Example 1 (Test)	31.389	7.053	2.462
Ceftin®Tablet (Reference)	27.4	7.0	3.0

The oral suspension of example 1 gives values of pharmacokinetic parameters for cefuroxime in human volunteers comparable to those given by Ceftin® tablets as shown in Table 3.

These data suggest the feasibility of substituting Ceftin® oral tablets with the oral suspension of example 1 in cases including pedriatic patients where tablets are not a convenient mode of administration.

WE CLAIM:

1. A dry powder pharmaceutical suspension composition suitable for use as a liquid suspension comprising granules containing cefuroxime axetil, at least one lubricant and at least one glidant.
2. A dry powder pharmaceutical suspension composition suitable for use as a liquid suspension comprising granules containing cefuroxime axetil, at least one lubricant and at least one glidant wherein the said composition exhibits better bioavailability as compared to Ceftin® oral suspension.
3. A dry powder pharmaceutical suspension composition suitable for use as a liquid suspension comprising granules containing cefuroxime axetil, at least one lubricant and at least one glidant wherein the said composition exhibits better bioavailability and is free of food effects.
4. The composition according to claim 1-3 wherein cefuroxime axetil comprises upto about 99.89% by weight of the granules.
5. The composition according to claim 1-3 wherein the lubricant is selected from stearic acid, calcium stearate, sodium stearyl fumarate and combinations thereof.
6. The composition according to claim 1-3 wherein the lubricant comprises from about 0.01% to about 10% by weight of the granules.
7. The composition according to claim 1-3 wherein the glidant is selected from colloidal silicon dioxide and talc.
8. The composition according to claim 1-3 wherein the glidant comprises about 0.1% to about 5% by weight of the granules.
9. The composition according to claim 1-3 wherein the composition further comprises suspending agents/viscosity enhancers, buffering agents, fillers, wetting agents, preservatives, flavouring agents and sweeteners.
10. The composition according to claim 9 wherein the suspending agent/viscosity enhancer is selected from cellulosic derivatives like hydroxypropyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, sodium carboxymethylcellulose; gums like xanthan gum, guar gum; polysaccharides like starch, pregelatinised starch; alginates like sodium alginate; acrylic acid copolymers like carbopols; polyvinylpyrrolidone and combinations thereof.
11. The composition according to claim 9 wherein the buffering agent is selected from monosodium citrate ,sodium citrate , citric acid and combinations thereof

12. The composition according to claim 9 wherein the filler is selected from sucrose, starch, lactose, microcrystalline cellulose and combinations thereof.

13. The composition according to claim 9 wherein the wetting agent is selected from sodium lauryl sulphate, polysorbates like tween 40, tween 60, tween 80, poloxamer and combinations thereof.

14. The composition according to claim 9 wherein the preservative is selected from methyl paraben, propyl paraben, sodium benzoate and combinations thereof.

15. The composition according to claim 9 wherein the flavouring agents/sweeteners are selected from grenadine flavour, tutti frutti flavour and peppermint flavour, aspartame, saccharine sodium, sucrose, sorbitol and sodium cyclamate and combinations thereof.

16. A method of forming a dry powder pharmaceutical suspension composition suitable for use as a liquid suspension comprising

granulating a mixture of cefuroxime axetil, at least one lubricant, at least one glidant by compaction/slugging; and

sizing the granules.

17. The method according to claim 16 wherein the granules are prepared by compaction.

18. The method according to claim 16 wherein cefuroxime axetil comprises upto about 99.89% by weight of the granules.

19. The method according to claim 16 wherein the lubricant is selected from stearic acid, calcium stearate, sodium stearyl fumarate and combinations thereof.

20. The method according to claim 16 wherein the lubricant comprises from about 0.01% to about 10% by weight of the granules.

21. The method according to claim 16 wherein the glidant is selected from colloidal silicon dioxide and talc.

22. The method according to claim 16 wherein the glidant comprises from about 0.1% to about 5% by weight of the granules.

23. The method according to claim 16 wherein the method further comprises mixing with the granules the other pharmaceutical excipients.

24. The method according to claim 23 wherein the other pharmaceutical excipients are selected from suspending agents/viscosity enhancers,

buffering agents, fillers, wetting agents, preservatives, flavouring agents and sweeteners.

25. The method according to claim 24 wherein the suspending agent/viscosity enhancer is selected from selected from cellulosic derivatives like hydroxypropyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, sodium carboxymethylcellulose; gums like xanthan gum, guar gum; polysaccharides like starch, pregelatinised starch; alginates like sodium alginate; acrylic acid copolymers like carbopols; polyvinylpyrrolidone and combinations thereof.

26. The method according to claim 24 wherein the buffering agent is selected from monosodium citrate , sodium citrate ,citric acid and combinations thereof.

27. The method according to claim 24 wherein the filler is selected from sucrose, starch, lactose, microcrystalline cellulose and combinations thereof.

28. The method according to claim 24 wherein the wetting agent is selected from sodium lauryl sulphate, polysorbates like tween 40, tween 60, tween 80, poloxamer and combinations thereof.

29. The method according to claim 24 wherein the preservative is selected from methyl paraben, propyl paraben, sodium benzoate and combinations thereof.

30. The method according to claim 24 wherein the flavouring agents/sweeteners are selected from grenadine flavour, tutti frutti flavour and peppermint flavour, aspartame, saccharine sodium, sucrose, sorbitol and sodium cyclamate and combinations thereof.

31. A method of dosing for infections treated with cefuroxime axetil which comprises administering the dry powder pharmaceutical suspension composition of cefuroxime axetil dissolved or suspended in an ingestible liquid comprising granules containing cefuroxime axetil, at least one lubricant and at least one glidant.

32. A method for the preparation of oral suspension of cefuroxime axetil substantially as described and exemplified herein.

Dated **30TH** day of **June, 2003.**

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

ABSTRACT

The present invention relates to a dry powder pharmaceutical suspension composition of cefuroxime axetil suitable for use as a liquid suspension wherein the composition has better bioavailability and is free of food effect. It also relates to a process for the preparation of such a composition.